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Brief report

Methohexitone, propofol and etomidate in electroconvulsive therapy for depression: A naturalistic comparison study

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Abstract

Background: Methohexitone has been the most widely used anaesthetic for electroconvulsive therapy (ECT). However, recent scarcity and erratic availability has led to use of other anaesthetics with differing effects upon ECT. We compared treatment parameters and response to ECT in patients anaesthetised with different anaesthetics in a routine clinical setting.
Methods: This was a naturalistic retrospective casenote analysis of 81 consecutive courses of ECT (total 659 treatments) for major depression.
Results: Three anaesthetics were compared: methohexitone ($n=34$), propofol ($n=13$) and etomidate ($n=34$). Mean seizure duration was lowest ($p<0.0001$) for propofol. However, mean stimulus charge was highest in the propofol group ($p<0.0001$) who required a greater increase in stimulus charge during the course of treatment and also experienced a greater proportion of failed seizures (≤ 15 s on EEG). Despite differing effects upon treatment parameters, choice of anaesthetic did not appear to significantly affect therapeutic response to ECT. Use of propofol may be associated with longer treatment course that could result in extra cost.
Limitations: This was a retrospective casenote study, in which patients were not randomised to anaesthetic and standardised outcome measures were not used. The small sample size in the propofol group may have reduced the power of the study to demonstrate other differences between propofol and the other anaesthetic groups. A formal economic analysis was not performed.
Conclusion: Individual anaesthetics differentially influence seizure duration and stimulus charge but final response to ECT appears not to be adversely affected.

Keywords: ECT; Anaesthesia; Methohexitone; Propofol; Etomidate; Depression

1. Introduction

ECT is the most powerful acute treatment available for severe depression (UK ECT Review Group, 2003). Anaesthesia plus muscle relaxation are integral parts of contemporary modified ECT. Muscle relaxation prevents muscle and skeletal trauma during seizures, while anaesthesia renders patients unaware of paralysis. The

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short-acting barbiturate methohexitone is considered first choice intravenous anaesthetic for ECT because of minimal anticonvulsant effects and limited haemodynamic response (APA Committee on Electroconvulsive Therapy, 2001; Ding and White, 2002; Wagner et al., 2005). Discontinuation of production in 1999 as *Brietal* (Eli Lilly, The Netherlands), and subsequent sporadic availability, has led to using other short-acting anaesthetics.

Recommended alternatives include propofol, etomidate and thiopentone (Royal College of Psychiatrists' Special Committee on ECT, 2002). Thiopentone is a barbiturate but longer-acting than methohexitone with increased recovery time, whereas etomidate and propofol are short-acting non-barbiturates. Etomidate causes myoclonic jerks that may be confused with seizures and prolonged use causes adreno-cortical insufficiency (Morris and McAllister, 2005). Propofol is associated with rapid recovery and less nausea but has more anticonvulsant effects (Walder et al., 2001).

It is important to know how different anaesthetics compare for ECT (Ding and White, 2002; Wagner et al., 2005). We compared effects of methohexitone, propofol and etomidate on seizure characteristics and response to ECT in depressed patients.

2. Materials and methods

2.1. Patients and casenote reviews

We reviewed casenotes of patients receiving ECT between May 1999 (when methohexitone supplies originally ceased) and December 2001 at the Maudsley and Bethlem Royal Hospitals, London. Propofol was used May to September 1999. Because of difficulties with seizure induction, ECT clinics switched to etomidate until methohexitone (*Brevimytal*, Lilly, Germany) became available in August 2000. Patients with major depressive disorder (American Psychiatric Association, 1994) were included. The Operational Criteria (OPCRIT) program generated DSM-IV diagnoses and symptom profiles (McGuffin et al., 1991). Demographic and clinical data were gathered: age, sex, ethnicity, concomitant drug treatment, previous ECT course, outpatient/inpatient status, and legal status (i.e. informal or treated under UK Mental Health Act 1983). Treatment resistance was measured by number of previous adequate courses of antidepressants and augmentation strategies. The study was approved by the Hospitals' Medical Director.

2.2. ECT treatments and anaesthesia

Bilateral ECT was administered twice weekly using the Thymatron DGx device (Somatics Inc., USA). The "age-method" (i.e. % charge = patient's age; 100% = 504 mC) (Swartz and Abrams, 1996) was used to estimate first treatment charge dose (mC) and thereafter dose was titrated using a standard protocol (Royal College of Psychiatrists, 1995) to ensure adequate seizure durations, i.e. ≥25 s on EEG. To provide a measure of dose titration during ECT courses, the difference between final and first stimulus charges was calculated for both absolute (mC) and relative (% change compared to first charge) changes. Both motor (direct visual observation) and EEG seizure durations were recorded. Number of treatments per course and inadequate (i.e. ≤15 s on EEG) or prolonged (i.e. ≥90 s on EEG) seizures were recorded.

Therapeutic response to ECT courses was estimated from casenotes using a simple scale: complete recovery, major improvement, minor improvement, no change, worse. If ECT led to discharge and resumption of normal activities, outcome was "complete recovery". If symptoms worsened, the patient became manic or suffered a major adverse event, the outcome was "worse". Patients were deemed responders if they rated "complete recovery" or "major improvement". The following post ictal side-effects were recorded as present/absent for individual treatments: confusion or amnesia, nausea, and severe headache.

2.3. Statistical analysis

Baseline variables were compared between the three anaesthetic groups using analysis of variance (ANOVA) for normally distributed variables and Fisher's exact test for binary variables. ANOVA was used to compare numbers of treatments per course, stimulus charges at first treatment, and differences in charges between final and first treatments. Treatment response was compared using Fisher's exact test.

Parameters for individual ECT treatments, including mean stimulus charge plus seizure durations, were compared using ANOVA with standard errors that are robust against correlations within clusters (Williams, 2000). Failed seizures and post ictal confusion were compared between groups using logistic regression analysis with robust standard errors. Clusters were declared to be patients to take account of correlations between measures from treatments of the same course/patient. Group comparisons were followed by post hoc pairwise comparisons if overall tests showed significance (Bonferroni adjusted significance level 5/3 = 1.7% for multiple comparisons).

Analyses were performed using Stata version 8 (StataCorp, College Station, Texas) and SPSS version 12.0 (SPSS Inc, Chicago). Data are presented as mean (standard deviation) or numbers (percentages) along with 95% confidence intervals for differences (CI).

3. Results

3.1. Patient characteristics

During the 32 month study period, 110 courses of ECT were administered. We identified casenotes for 100 courses (90.9%) given to 94 patients. Of these, 84 courses were given to 83 patients for depression. Three courses were excluded because more than one anaesthetic was used. Of these depressed patients, those who received methohexitone, propofol or etomidate comprised 81 ECT courses for 81 patients (see Table 1). Complete ECT records were available for 80 patients who received 646 treatments in total; details were unavailable for one patient who received 13 treatments using propofol.

Except for age ($p=0.03$), there were no significant differences between groups for pre-treatment variables and, though not randomised, groups were otherwise reasonably well-balanced. Age was lowest in the methohexitone group and highest in the propofol group.

3.2. ECT treatment courses

Methohexitone, propofol and etomidate were used at 1.18(0.19) mg/kg, 1.34(0.25) mg/kg and 0.29(0.15) mg/kg, respectively (recommended doses being 0.75–1.0, 0.75–2.5 and 0.15–0.3 mg/kg, respectively); suxamethonium was used at 0.65(0.16), 0.59(0.08) and 0.64(0.16) mg/kg for the methohexitone, propofol and etomidate groups respectively (recommended dose, 0.5–1.0 mg/kg (Ding and White, 2002)).

Mean number of treatments per ECT course (see Table 2) did not differ significantly between groups. There was no significant difference between groups for treatment response. There was an unusually high response rate of 92.31% in the propofol group; this may be artefactual resulting from the smaller sample size. Response rate of about 60% in the other groups is similar to recent trial findings (Eranti et al., 2007).

3.3. ECT treatment parameters

First stimulus charge was greater for propofol ($p<0.0001$) but similar in methohexitone and etomidate

Table 2
ECT courses — number of treatments and response

	Methohexitone ($n=34$)	Propofol ($n=13$)	Etomidate ($n=34$)	Statistical analysis
Number of treatments per course	7.76 (3.17)	9.62 (5.71)	8.00 (5.58)	$df(2,78)$, $F=0.75$, $p=0.48$
Treatment response [a]	20 (58.82%)	12 (92.31%)	21 (61.76%)	Fisher's exact test, $p=0.08$

Data are mean (SD) or number (%).
[a] Data include complete and major improvement.

Table 1
Baseline characteristics

	Methohexitone ($n=34$)	Propofol ($n=13$)	Etomidate ($n=34$)	Statistical analysis
Age (years)	59.21 (15.28)	72.08 (7.58)	63.18 (15.86)	$df(2,78)$, $F=3.65$, $p=0.03$*
Sex: male	9 (26.5%)	2 (15.4%)	10 (29.4%)	$p=0.57$
Ethnicity: white British	30 (88.2%)	11 (84.6%)	30 (88.2%)	n/a
In-patient	32 (94.1%)	12 (92.3%)	33 (97.1%)	n/a
Informal patients	19 (55.9%)	9 (69.2%)	18 (52.9%)	$p=0.72$
Previous ECT	19 (55.9%)	10 (76.9%)	21 (61.8%)	$p=0.31$
Level of treatment resistance (>2 failed treatments)	19 (55.9%)	7 (53.8%)	14 (41.2%)	$p=0.32$
Number of psychotropic medications	2.18 (0.94)	2.15 (0.80)	1.91 (0.83)	$df(2,78)$, $F=0.87$, $p=0.42$*
SSRI	11 (32.4%)	4 (30.8%)	14 (41.2%)	$p=0.86$
TCA	4 (11.8%)	4 (30.8%)	6 (17.6%)	$p=0.13$
MAOI	1 (2.9%)	1 (7.7%)	1 (2.9%)	$p=0.85$
Other antidepressant	12 (35.3%)	5 (38.5%)	10 (29.4%)	$p=0.93$
Lithium	2 (5.9%)	4 (30.8%)	4 (11.8%)	$p=0.14$
Carbamazepine	3 (8.8%)	2 (15.4%)	1 (2.9%)	$p=0.43$
Other mood stabilisers	3 (8.8%)	1 (7.7%)	1 (2.9%)	$p=0.67$
Benzodiazepines	12 (35.3%)	1 (7.7%)	7 (20.6%)	$p=0.09$
Typical neuroleptics	6 (17.6%)	2 (15.4%)	7 (20.6%)	$p=0.70$
Atypical antipsychotics	19 (55.9%)	4 (30.8%)	12 (35.3%)	$p=0.07$
Patients with psychosis	12 (35.3%)	5 (38.5%)	16 (47.1%)	$p=0.78$

Data are mean (SD) or number (%) of patients. Data were analysed by Fisher's exact test or, where indicated *, by ANOVA. n/a, statistical analysis not appropriate; SSRI, selective serotonin reuptake inhibitor; TCA, tricyclic antidepressant; MAOI, monoamine oxidase inhibitor.

groups (see Table 3). This reflects the greater age of the propofol group and use of "age-method" to calculate first treatment charge.

On analysing all treatments, much higher mean stimulus charges were required throughout treatment courses using propofol ($p<0.0001$). Post hoc tests

Table 3
Individual ECT treatment parameters and side-effects

	Methohexitone ($n=264$)	Propofol ($n=110$)	Etomidate ($n=272$)	Formal overall group comparison	Post hoc tests
Number of patients	34	12	34		
ECT parameters					
Stimulus charge (mC)	273.76 (133.11)	675.63 (203.85)	209.86 (116.91)	$df(2,79)$, $F=24.71$, $p<0.0001$	Methohexitone vs. propofol: $p<0.0001$ Methohexitone vs. etomidate: $p=0.05$ Propofol vs. etomidate: $p<0.0001$
First stimulus charge (mC) per course	280.09 (77.61)	495.58 (112.72)	276.09 (79.27)	$df(2,77)$, $F=34.05$, $p<0.0001$	Methohexitone vs. propofol: $p<0.0001$ Methohexitone vs. etomidate: $p=0.85$ Propofol vs. etomidate: $p<0.0001$
Difference between final and first stimulus charges (mC) per course	0.79 (166.84)	243.67 (210.60)	−52.35 (146.69)	$df(2,77)$, $F=14.34$, $p<0.0001$	Methohexitone vs. propofol: $p<0.0001$ Methohexitone vs. etomidate: $p=0.19$ Propofol vs. etomidate: $p<0.0001$
% difference between final and first stimulus charges per course	0.28 (62.06)	52.55 (49.37)	−16.93 (64.34)	$df(2,77)$, $F=5.68$, $p=0.005$	Methohexitone vs. propofol: $p=0.013$ Methohexitone vs. etomidate: $p=0.25$ Propofol vs. etomidate: $p=0.001$
Motor seizure duration (s)	27.78 (15.59)	17.32 (8.59)	31.93 (29.07)	$df(2,79)$, $F=13.63$, $p<0.0001$	Methohexitone vs. propofol: $p<0.0001$ Methohexitone vs. etomidate: $p=0.13$ Propofol vs. etomidate: $p<0.0001$
EEG seizure duration (s)	39.31 (30.06)	28.01 (14.41)	44.57 (28.21)	$df(2,79)$, $F=10.20$, $p<0.0001$	Methohexitone vs. propofol: $p=0.003$ Methohexitone vs. etomidate: $p=0.14$ Propofol vs. etomidate: $p<0.0001$
Failed seizures (≤15 s)	11 (4.2%)	13 (11.8%)	12 (4.4%)	$df(2)$, $\chi^2=7.14$, $p=0.028$*	Methohexitone vs. propofol: $p=0.02$ Methohexitone vs. etomidate: $p=0.90$ Propofol vs. etomidate: $p=0.02$
Prolonged seizures (≥90 s)	4 (1.5%)	0 (0%)	7 (2.6%)	n/a	
Post ictal side-effects					
Confusion/amnesia	64 (24.2%)	44 (40.0%)	48 (17.6%)	$df(2)$, $\chi^2=1.97$, $p=0.37$*	
Nausea	16 (6.1%)	0 (0%)	11 (4.0%)	n/a	
Severe headache	0 (0%)	0 (0%)	10 (3.7%)	n/a	

Data are mean (SD) or number (%). Data were analysed by ANOVA or, where indicated *, by logistic regression. mC, millicoulomb; n/a, statistical analysis not appropriate.

showed significant differences in stimulus charge (mC) with propofol compared to methohexitone (95% CI= 268.42 to 535.32, $p<0.0001$) or etomidate (95% CI= 333.53 to 598.01, $p<0.0001$) while there was a non-significant trend for lower charge with etomidate compared to methohexitone (95% CI=1.57 to 126.22; $p=0.05$). In addition, the difference between final and first stimulus charges during the course was significantly greater with propofol for both absolute ($p<0.0001$) and relative (%) differences ($p=0.005$). Post hoc tests showed significantly greater differences in % change in charges between final and first treatments with propofol compared to methohexitone (95% CI=11.19 to 93.33, $p=0.013$) or etomidate (95% CI=28.41 to 110.55, $p=0.001$). Although mean charges actually decreased during treatment courses when using etomidate, there was not a significant difference when compared to % change in the methohexitone group (95% CI=−46.88 to 12.45, $p=0.25$). In summary, while first stimulus charges were higher with propofol compared to the other anaesthetics, both mean charge and dose titration were significantly greater for propofol during the course of ECT.

Despite substantially greater charges when using propofol, both motor and EEG seizures were significantly shorter with propofol ($p<0.0001$ for both measurements). Post hoc analyses revealed significant differences in motor seizure duration between propofol and both methohexitone (95% CI=5.36 to 15.56, $p<0.0001$) and etomidate (95% CI=8.68 to 20.55, $p<0.0001$). Similarly, when compared to propofol, EEG seizures were significantly shorter with methohexitone (95% CI=3.87 to 18.67, $p=0.003$) or etomidate (95% CI=9.16 to 23.94, $p<0.0001$).

Prolonged seizures occurred too infrequently for formal analyses. It is interesting to note there were more prolonged seizures with etomidate (2.6%) than methohexitone (1.5%), while none occurred with propofol. There was a significantly greater proportion of failed seizures with propofol (11.8%) with a trend for fewer failed seizures with both methohexitone (4.2%) and etomidate (4.4%) compared to propofol.

3.4. Reported side-effects

The proportion of treatments with post ictal confusion/amnesia did not differ significantly between groups ($p=0.37$; see Table 3). Post ictal nausea was reported after a small proportion of treatments when using methohexitone (6.1%) or etomidate (4.0%) but not for propofol. Severe headache was reported after 3.7% of treatments using etomidate while there were none with the other anaesthetics. No major adverse events were reported.

4. Discussion

We found that although significantly greater stimulus charges were used with propofol, compared to methohexitone or etomidate, seizure durations were significantly shorter with propofol. During an ECT course seizure threshold can rise necessitating increased charge to ensure adequate and therapeutic seizures (Royal College of Psychiatrists, 2005). Compared to methohexitone and etomidate, even allowing for larger first stimulus charges used in the propofol group due in part to older age, propofol was associated with larger charges and a much greater requirement for titrating stimulus dose upwards. In addition, there was a strong trend for more failed seizures with propofol. Despite these findings, treatment response with propofol was no worse than with methohexitone or etomidate.

A recent meta-analysis of randomised trials comparing methohexitone with propofol concluded that propofol was associated with significantly shorter seizures but it was not possible to establish whether this affected side-effects or outcome (Walder et al., 2001). Direct comparisons of etomidate with methohexitone found no differences in seizure duration (Gran et al., 1984; Kovac and Pardo, 1992). In a retrospective study comparing etomidate ($n=36$) with propofol ($n=29$), seizure duration was significantly shorter with propofol although again total charge used and increase in charge between first and last treatments were both significantly longer; ECT course length was also significantly longer, requiring on average an extra two treatments with propofol (Patel et al., 2006). Swaim et al. (2006), in their naturalistic retrospective comparison ($n=95$, 1042 treatments) of methohexitone, propofol and thiopentone, also found significantly shorter seizures with propofol compared to methohexitone plus significantly greater stimulus charge with propofol compared to thiopentone. In one small ($n=10$, 90 treatments) randomised cross-over study, in which methohexitone was compared with both propofol and etomidate, seizure durations were longest with etomidate and shortest with propofol (Avramov et al., 1995).

For response to ECT, seizure duration may not be as relevant as ensuring charge is suitably suprathreshold (Sackeim et al., 1993). However, definition of seizure threshold is based upon a minimal seizure duration and in routine practice measuring seizure duration is a useful surrogate marker for therapeutic effectiveness (American Psychiatric Association Committee on Electroconvulsive

Therapy, 2001). Thus it has been suggested that propofol may be useful when patients, especially adolescents and young adults, have a very low seizure threshold or prolonged seizures (Bailine et al., 2003). Alternatively, etomidate may be indicated when seizures are too short and possibly sub-therapeutic despite maximum stimuli (Benbow et al., 2002; Datto et al., 2002; Khalid et al., 2006).

ECT anaesthetic practice can be tailored further. For example, because propofol causes less haemodynamic changes than methohexitone, etomidate or thiopentone, it may be anaesthetic of choice for patients with cardiac disease (Avramov et al., 1995; Geretsegger et al., 1998; Kadoi et al., 2003). In addition, propofol is associated with less nausea and vomiting after ECT (Bailine et al., 2003) as found in the present study.

4.1. Limitations

This study is limited by retrospective design and associated danger of confounding. However, many of our results parallel previous studies, while allowing novel comparisons under real world conditions. Not using standardised measures may account for low reporting rates for post ictal side-effects. Reports of post ictal confusion/amnesia were similar to previous studies (Sackeim et al., 1987; Tecoult and Nathan, 2001) but reports of headaches seemed low, i.e. only 0–3.7%. Headache has been reported to occur in up to 60% of patients (Leung et al., 2003). It may be that patients do not complain of headache unless very severe and enquired about.

The lower number of patients in the propofol group may have led to the study being underpowered to detect other differences between methohexitone/etomidate and propofol groups. For example, as previously reported (Patel et al., 2006), one might predict an increased number of treatments to compensate for substantially shorter seizures and increased failed seizures associated with propofol. In the present study, there was an increase on average of at least one extra treatment with propofol compared to methohexitone/etomidate but this did not achieve statistical significance. However, if true this would be associated with increased ECT costs (£211 per treatment (McLoughlin et al., 2007)) plus admission expenses.

Because initial stimulus charges were estimated using an "age-method" (Swartz and Abrams, 1996), seizure thresholds were not empirically determined. Compared to methohexitone and etomidate, propofol was associated with substantially higher stimulus charges but shorter seizures during ECT courses. It is not clear whether such high charges are necessary with propofol. Previous studies have not found a significant difference between empirically determined seizure thresholds when comparing propofol with methohexitone (Scott and Boddy, 2002) or etomidate (Patel et al., 2006). It is also not clear whether seizure threshold rises more during a course of ECT when using propofol. It may be that the relatively shorter seizures occurring with propofol are induced by supra-threshold charges and therefore are probably therapeutic. Indeed, despite its effects on treatment parameters, we and others have found that the therapeutic outcome with propofol is not worse than when using other anaesthetics.

4.2. Conclusions

Individual anaesthetics have significantly different effects upon ECT parameters such as seizure length and stimulus charge. Propofol has more pronounced effects that can result in technical difficulties but that do not adversely affect response. However, compared to methohexitone and etomidate, propofol may be associated with longer treatment course and this could have cost implications. Many of these problems could be avoided by establishing seizure threshold in the first session rather than using the "age-method".

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Conflict of interest

The authors have no conflicts of interest to declare.

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